


# Bevacizumab-associated intestinal perforation and perioperative complications in patients receiving bevacizumab

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## Abstract

**Aim:** The purposes of this study are to present cases of emergency surgery in which gastrointestinal perforation occurred during bevacizumab administration, consider the indications for emergency surgery, and examine the safety of scheduled surgery after a washout period for bevacizumab.

**Methods:** (a) We retrospectively investigated seven patients who underwent emergency surgery for bevacizumab-associated intestinal perforation. (b) We investigated 104 patients with advanced colorectal cancer treated with neoadjuvant therapy who underwent surgery from 2008 to 2018, retrospectively.

**Results:** (a) In the seven patients undergoing emergency surgery for gastrointestinal perforation, the median bevacizumab administration and washout periods were 16 weeks and 24 days, respectively. A stoma was created in all patients except in those who were not candidates. Two patients developed postoperative abdominal abscesses, and two patients died from perioperative sepsis and gastrointestinal bleeding, respectively; both of these patients had poor performance status. (b) In patients receiving bevacizumab ( $n = 45$ ) and patients treated with bevacizumab-free regimens as neoadjuvant therapy ( $n = 59$ ), 31 and 52 patients received chemoradiotherapy, respectively. We found no correlation with postoperative complications with or without bevacizumab.

**Conclusion:** The surgical indications should be considered carefully in patients with gastrointestinal perforation secondary to bevacizumab administration. Meanwhile, after appropriate cessation time, scheduled surgery following bevacizumab administration is feasible.

## KEYWORDS

bevacizumab, cancer, emergencies, perforation, postoperative complications

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## 1 | INTRODUCTION

Bevacizumab is a molecular-targeted drug used for colorectal cancer, non-small cell lung cancer, breast cancer, and malignant glioma.<sup>1-3</sup> Vascular endothelial growth factor (VEGF) plays an important role in tumor proliferation, invasion, and metastasis by promoting angiogenesis.<sup>4</sup> Furthermore, VEGF is known to be associated with recurrence and prognosis,<sup>2</sup> and its inhibition is an important factor for treatment.<sup>5</sup> Bevacizumab specifically binds to VEGF-A and inhibits its binding to VEGF receptor (VEGFR)-1 and VEGFR-2, thereby inhibiting VEGF signal transduction.<sup>3</sup> In colorectal cancer, many patients present with advanced disease or develop metastases within the first years after curative surgery,<sup>6</sup> and bevacizumab has contributed to meaningful improvements in survival in patients with advanced colorectal cancer in recent years.<sup>7-9</sup> In Japan, some regimens including bevacizumab are recommended as first-line therapy for unresectable colorectal cancer.<sup>10</sup> Furthermore, bevacizumab is used in both palliative and neoadjuvant settings.<sup>1</sup> However, bevacizumab has also been associated with significant side effects.<sup>11-13</sup> In patients who have not undergone surgery, bevacizumab has been associated with hypertension (3.0%-15.0%), proteinuria (0.7%-1.0%), diarrhea (4.0%-39.9%), arterial (0.9%-10.0%) and venous (2.7%-14.9%) thromboembolism, hemorrhage (1.4%-5.0%), and gastrointestinal perforation (0.6%-2.9%).<sup>3,14-16</sup> Postoperatively, gastrointestinal perforation (2.0%-20.0%), wound infection (1.5%-11.1%), wound healing issues (2.0%-9.7%), hemorrhage (2.7%), and anastomotic dehiscence (2.0%) are attributed to the use of bevacizumab.<sup>15</sup> The inhibition of VEGF signal transduction, which affects angiogenesis, may impact healing and cause gastrointestinal perforation.<sup>17</sup> Bowel perforation is a serious complication, and immediate recognition followed by surgical intervention is the best management for this potentially fatal complication.<sup>1,5,13</sup> The fatality rate in patients with gastrointestinal perforation treated with bevacizumab was reported to be as high as 20%.<sup>2,18</sup> In this report, we investigated patients undergoing emergency surgery who developed gastrointestinal perforation during bevacizumab administration, and patients with advanced colorectal cancer who could safely undergo surgery after a washout period for bevacizumab.

## 2 | METHODS

This study was performed in accordance with the Helsinki Declaration of the World Medical Association (2013 revision). This retrospective study enrolled seven patients who underwent emergency surgery for bevacizumab-associated intestinal perforation (Study 1). Furthermore, we retrospectively investigated 104 patients with advanced colorectal cancer treated with neoadjuvant therapy and surgery at Tokushima University Hospital from 2008 to 2018 (Study 2). Of these, we included 45 patients treated with bevacizumab-including regimens as neoadjuvant therapy and 59 patients treated with bevacizumab-free regimens. Thirty patients in the bevacizumab group received radiotherapy with S-1/Oxaliplatin/Bevacizumab (SOX + Bev) in a clinical study

(UMIN000006937). The radiation dose at CRT was 40 Gy for all SOX + Bev, S-1, and UFT regimens.

## 2.1 | Statistical analysis

We used the Chi-square test, and *P*-values < .05 were considered statistically significant. All statistical analyses were performed using JMP version 13 statistical software (SAS Institute Inc).

## 3 | RESULTS

### 3.1 | Study 1. Bevacizumab-induced intestinal perforation

Table 1 shows the details of the seven patients who developed bevacizumab-induced intestinal perforation and who underwent emergency surgery. The median number of administration cycles was five (range: 3-30 cycles), and the median cessation time was 24 days (range: 6-35 days). All seven patients underwent emergency surgery, and a stoma was created in all patients except those in whom the perforation site was unknown or ostomy was not possible because of the presence of cancerous peritonitis. Two patients developed abdominal abscess postoperatively, which resolved with drainage. Two additional patients with poor performance status before perforation died from perioperative sepsis and gastrointestinal bleeding, respectively. In the five surviving patients, additional chemotherapy or radiation therapy for the primary tumor could be given in four patients.

### 3.2 | Study 2. Comparison of patients receiving and not receiving bevacizumab

Table 2 shows a comparison of bevacizumab-administrated patients and patients treated with bevacizumab-free regimens as neoadjuvant therapy with or without radiotherapy. In the without-radiotherapy group (*n* = 21), 14 patients received bevacizumab. In contrast, 31 patients were treated with bevacizumab in the chemoradiotherapy group. We found no correlation between bevacizumab administration and the occurrence of postoperative complications of Clavien-Dindo classification grade III or higher. Additionally, patients in the bevacizumab-free group developed complications such as suture leakage and stoma necrosis.

## 4 | DISCUSSION

This report revealed that planned surgery is feasible following bevacizumab administration with appropriate cessation time. In addition, in patients developing gastrointestinal perforation during bevacizumab administration, it is desirable to construct a stoma

TABLE 1 Patients with bevacizumab-induced intestinal perforation

Pt.#	Primary disease	Primary site	PS	Regimen (+Bev)	Administration (cycles)	Days since last administration	Perforation site	Operative procedures	Postoperative complications	CD	Survival days	Further chemo/ radio therapy
1	Rectum	-	2	FOLFOX	7	24	Panperitonitis	Lavage and drainage	None	-	317	Yes
2	Rectum	+	2	FOLFOXIRI	3	33	Transverse colon	Colostomy	None	-	597	Yes
3	Lung	-	2	PEM	5	10	Descending colon	Hartmann's operation	Intra-abdominal abscess	IIla	205	Yes
4	Descending colon	+	2	FOLFOXIRI	30	9	Tumor	Hemicolectomy and colostomy	Iliopsoas abscess	IIlb	152	No
5	Appendix	+	2	mFOLFOX6	5	6	Transverse colon	Lavage and drainage	None	-	92	Yes
6	Uterine cervix	+	3	TC	5	35	Small intestine	Jejunostomy	Intestinal bleeding	V	11	No
7	Cecum	+	3	IRIS	10	26	Tumor	Ileostomy	Sepsis, SSI	V	33	No

Abbreviations: Bev, bevacizumab; FOLFOX, fluorouracil + levofolinate + oxaliplatin; FOLFOXIRI, fluorouracil + levofolinate + oxaliplatin + irinotecan; IRIS, irinotecan + S-1; mFOLFOX6, fluorouracil + levofolinate + oxaliplatin; PEM, pemetrexed; Pt., patient; SSI, surgical site infection; TC, paclitaxel + carboplatin.

without anastomosis, and it is necessary to consider the patient's current disease status and performance status regarding the surgical indications. Bevacizumab, a monoclonal antibody to soluble VEGF, has an important and evolving role in improving outcomes for patients with unresectable colorectal cancer.<sup>7,15</sup> Molecularly-targeted agents are generally safe and less toxic than cytotoxic agents<sup>4,19,20</sup>; however, previous reports showed that bevacizumab administration is a risk factor for gastrointestinal perforation, which is partly related to primary tumor perforation.<sup>8,12</sup> The risk factors for gastrointestinal perforation include high-dose administration of bevacizumab, acute diverticulitis, bowel obstruction, recent history of sigmoidoscopy or colonoscopy, history of pelvic or abdominal irradiation, carcinomatous peritonitis, peptic ulcer, and administration of steroids or nonsteroidal anti-inflammatory drugs.<sup>19,21</sup>

Bevacizumab exerts antitumor effects by causing ischemic changes, such as microvascular involution in tumors and suppression of neovascularization in the tumor tissue.<sup>2,3</sup> The effect of both neovascularization antagonism and reducing the tumor tissue framework pressure normalizes the tumor vasculature and improves the delivery of the chemotherapeutic drugs into the tumor.<sup>2,3</sup> Several mechanisms have been described to explain the development of bevacizumab-related gastrointestinal perforation. In the first, the inhibition of VEGF by bevacizumab could cause a decrease in vascular density, disorders of vasoconstriction secondary to the arterial thrombus, and embolism as a result of failure of blood vessel structure and functional disorders.<sup>2,19</sup> The second possible mechanism is related to the gastrointestinal mucosa. Constant gastrointestinal wall proliferation and healing are dependent on microcirculation, protection with nitrous oxide, and normal platelet function, all of which depend on VEGF.<sup>2</sup> Intestinal healing after damage such as that following surgery, or ulcers, is also dependent on these processes. According to these mechanisms, nonsteroidal anti-inflammatory drugs are a risk factor for bevacizumab-related gastrointestinal perforation. In a previous animal experimental study, preoperative administration of bevacizumab inhibited angiogenesis and also decreased  $\alpha$ -smooth muscle actin accumulation and collagen deposition in the intestinal anastomotic tissue.<sup>1</sup> The third possible mechanism is, ironically, the great efficacy of bevacizumab to reduce tumor volume. Tumor structure may provide some stability to the intestinal wall itself, and tumor death caused by bevacizumab creates perforation.<sup>2</sup> Of gastrointestinal perforations induced by bevacizumab, 80% occur within 6 months after initial bevacizumab administration.<sup>21</sup> The most common site of perforation is the colon, followed by the small intestine and stomach.<sup>13,21</sup> In this study, intestinal perforations occurred within 6 months after initial bevacizumab administration in all patients, and primary tumor perforation occurred in two patients. As a risk factor, one patient had cancerous peritonitis.

The timing of therapy relative to surgery has been shown to be critically important because of the long half-life of bevacizumab.<sup>15</sup> Because the half-life of bevacizumab is about 20 days,<sup>11,19,22</sup> it has been recommended that bevacizumab be delayed a minimum of

**TABLE 2** Comparison of patients receiving and not receiving bevacizumab

Factors		CRT (-)			CRT (+)		
		Bev. (-) (n = 8)	Bev. (+) (n = 14)	P value	Bev. (-) (n = 51)	Bev. (+) (n = 31)	P value
Sex	Male/Female	7/1	10/4	.37	35/16	19/12	.47
Location	Colon/Rectum	3/5	9/5	.22	0/51	0/31	
fStage	I/II/III/IV	1/2/1/4	0/1/1/12	.26	20/15/10/5	14/6/10/1	.35
Regimen	Sing./Doub./Trip.	0/5/3	0/10/4	.67	51/0/0	0/30/1	<.001
Stoma	-/+	2/6	5/9	.61	2/49	0/31	.26
Postop. Complications (CD ≥ III)	-/+	6/2	13/1	.24	45/6	28/3	.77
Leakage	-/+	7/1	14/0	.18	50/1	31/0	.43
Ileus	-/+	7/0	13/1	.47	49/2	30/1	.87
Pelvic abscess	-/+	8/0	14/0		50/1	29/2	.29
Stoma necrosis	-/+	8/0	14/0		50/1	31/0	.43
Thoracic empyema	-/+	8/0	14/0		50/1	31/0	.43
Plural effusion	-/+	7/1	14/0	.18	51/0	31/0	

Abbreviations: Bev. (-), not receiving bevacizumab; Bev. (+), receiving bevacizumab; CD, Clavien–Dindo; CRT, chemoradiotherapy; Doub., double; Postop, postoperative; Sing., single; Trip., triple.

28 days between surgery and treatment; however, many advocate for a drug-free interval of a minimum of 6 weeks and some as high as 60 days to help prevent wound-healing complications.<sup>12,15,20,22</sup> In this study, all patients except one underwent a 4-week cessation period with planned surgery, and none developed severe perioperative complications. In patients undergoing surgery within 4 weeks of the final administration of bevacizumab, only one catheter-related infection occurred. Regarding anticancer drugs used in combination with bevacizumab, significant difference of number of regimens was observed between Bev (+) group and (-) group in the chemoradiotherapy group. Several previous meta-analyses of bevacizumab randomized controlled trials showed no significant difference in perforation rates between different concomitant medications or regimens.<sup>23,24</sup> Also, in this study, there was no correlation between the number of regimens and postoperative complications with or without radiation therapy (data not shown).

The incidence of gastrointestinal perforation after radiotherapy has been reported to be around 2% for doses below 50 Gy and 14% above 50 Gy<sup>25</sup>; however, in this study, all patients underwent 40 Gy irradiation. Furthermore, the interval from irradiation to surgery was 6–8 weeks in all cases, but according to past meta-analysis, the complication rate was the same even if the interval was longer than 6–8 weeks.<sup>26</sup>

In patients undergoing emergency surgery, we constructed a stoma unless the patient was not a candidate. As a result, postoperative abdominal abscess occurred in only two patients and resolved with drainage. Two patients died secondary to complications unrelated to the anastomosis, and both had poor preoperative performance score. Regarding the management of bevacizumab-related gastrointestinal perforation, there is a risk of serious complications

after emergency surgery, and only one study discussed options for nonsurgical treatment<sup>27</sup>; therefore, it is necessary to carefully consider the surgical indications.

The main limitations of this study are the limited number of patients and patients' different backgrounds. Because bevacizumab is used in a growing number of people with metastatic colorectal cancer, surgeons will have to operate increasingly frequently in this high-risk population.<sup>11</sup> In conclusion, we recommend that the surgical indications be considered carefully in patients with severe gastrointestinal perforation secondary to bevacizumab administration. However, after an appropriate cessation time, scheduled surgery is feasible following bevacizumab administration.

## DISCLOSURE

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Author Contribution: Toshiaki Yoshimoto: Manuscript writing, analysis, operating surgeon. Kozo Yoshikawa: Manuscript editor, operating surgeon. Jun Higashijima: Operating surgeon. Tomohiko Miyatani, Takuya Tokunaga, Masaaki Nishi, Chie Takasu, Hideya Kashihara and Yukako Takehara: Attending physicians of the presented patient. Mitsuo Shimada: Supervisor.

Ethical Approval: All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki declaration of 1964 and later revisions (Review board: Tokushima clinical trial management system (ToCMS); approval number: 3215). Informed consent or substitute for it was obtained from all patients for being included in the study.

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